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# Chronic Hepatitis C Treatment: A Systematic Review

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## ABSTRACT

**Background:** Chronic hepatitis C (CHC) infection affects almost 3% of the global population and can lead to cirrhosis, liver failure, and hepatocellular carcinoma in a significant number of those infected. Thus, there is a complelling need to develop and introduce new therapeutics with a direct-acting antiviral effect in order to target various stages of the HCV lifecycle for HCV eradication without concomitant interferon.

**Study Objective:** to provide treatment recommendations for chronic HCV for specialists and generalists based on published evidence.

**Methods:** A literature search of Web of Science, Scopus, Embase, Agricola, Cochrane Library, Cinahl Plus, Google Scholar, and Oaister was conducted from 1990 to 2016, records were filtered according to the Inclusion criteria and 27 hits were yielded.

**Results:** Hepatitis C virus genotype 1 is more difficult to cure than genotype 2 or genotype 3. Patients with HCV genotype 1 should receive treatment with sofosbuvir + pegylated interferon + ribavirin because of the shorter duration of therapy and high rates of SVR (89%-90%). Simeprevir + pegylated interferon + ribavirin is an alternative for patients with HCV genotype 1 (SVR, 79%-86%). Patients with HCV genotypes 2 and 3 should receive therapy with sofosbuvir + ribavirin alone (SVR for genotype 2, 12 weeks' duration: 82%-93%; SVR for genotype 3, 24 weeks' duration, 80%-95%). Patients with HIV-HCV coinfection and patients with compensated cirrhosis (ie, cirrhosis but preserved synthetic liver function) should receive the same treatment as HCV-monoinfected patients. **Conclusion:** A growing body of evidence suggests that recently developed HCV combined treatment modalities have transformed chronic HCV into a routinely curable disease being relatively available and well tolerated ,which can potentially reduce the need for liver transplantation and reduce HCV-related mortality. Treatment protocol for genotype1 is based on a combined regimen of Pegylated interferons with ribavirin and sofosbuvir or simeprevir while Sofosbuvir with ribavirin alone should be used to treat patients infected with HCV genotypes 2 and 3. Patients coinfected with human immunodefiency virus and HCV genotype 1 should be treated for HCV with pegylated interferons, ribavirin, and sofosbuvir by a physician with experience in treating this particular group of patients and familiar with potential drug interactions.

**Keywords:** Hepatitis C, Treatment, SVR , HCV genotype, Simeprevir, Ribavirin.

## INTRODUCTION

Hepatitis C virus (HCV) is a globally prevalent pathogen and a leading cause of death and morbidity[1] .The most recent estimates of disease burden show an increase in seroprevalence over the last 15 years to 2.8%, equating to >185 million infections worldwide [2] . Acute HCV infection turns into chronic infection in 70%–80% of cases, and 20%–25% of those with Persistent HCV infection is associated with the development of liver cirrhosis, hepatocellular cancer, liver failure, and death[3] ,and HCV is now the most common cause of death in HIV-positive patients on highly active antiretroviral therapy [4] .

HCV infection may present different geographical characteristics, which may be associated with ethnical / race and environmental factors such as HCV genotype and coinfection with other pathogenic agents [5] . The prevalence of hepatitis C is particularly high in subpopulations of



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incarcerated people, homeless people, veterans, and patients infected with human immunodeficiency virus (HIV) (**Table 1**) [6].

**Table 1: Prevalence of HCV Genotypes and of HCV Infection in the United States by Risk Factor.**

| **HCV genotypes** | |
|---|---|
| | Prevalence of HCV, % |
| **Genotype 1a** | 36-55 % |
| **Genotype 1b** | 25-23 % |
| **Genotype 2** | 13-16 % |
| **Genotype 3** | 8-13% |
| **Genotype 4** | 1-2% |
| **HIV infection** | |
| **Intravenous** | drug |
| **IV injection** | 58% |
| **Homeless2** | 22-53% |
| **Prisoner2** | 23-41% |
| **Veteran2** | 3-18% |
| **Risk Factors** | |
| **Birth cohort** | |
| **1945-1949** | 1.58 % |
| **1950-1965** | 3.61% |
| **1966-1970** | 1.97% |
| **1. Ethnicity** | |
| **White** | 2.8% |
| **Black** | 5.60% |
| **Hispanic** | 2.70% |
| **2. Sex** | |
| **Male** | 3.90% |
| **Female** | 2.10% |

HCV, hepatitis C virus; HIV, human immunodeficiency virus.

There are 6 known genotypes of HCV. HCV genotype 1 is the most prevalent worldwide, comprising 83.4 million cases (46.2% of all HCV cases), approximately one-third of which are in East Asia. Genotype 3 is the next most prevalent globally (54.3 million, 30.1%); genotypes 2, 4, and 6 are responsible for a total 22.8% of all cases; genotype 5 comprises the remaining <1%. While genotypes 1 and 3 dominate in most countries irrespective of economic status, the largest proportions of genotypes 4 and 5 are in lower-income countries [7].

Although there is no difference in the risk of cirrhosis according to genotype, genotype 3 is associated with a higher rate of hepatic steatosis7 and genotype 1b is associated with a higher rate of hepatocellular carcinoma [8]. Hepatitis C virus (HCV) is a major cause of chronic hepatitis and hepatic fibrosis that progresses in some patients to cirrhosis and hepatocellular carcinoma (HCC). Almost all of patients life-threatenig complications of chronic HCV such as hepatocellular carcinoma, bleeding esophageal varices, life-threatening infections, hepatic synthetic failure, and intractable ascites occur in patients with cirrhosis. Unfortunately, it is difficult to identify reliably those patients who will ultimately develop advanced liver disease. Management of chronic hepatitis C is further complicated because therapeutic interventions are more successful in patients with early than in those with advanced disease, so that therapy is best applied before complications of chronic liver disease appear [9].

The natural history of HCV-related liver disease is variable among individuals, but without effective treatment strategies, hepatitis C-related morbidity and mortality is expected to increase significantly in

the coming years . Accordingly, current hepatitis C therapies are aimed at achieving eradication of HCV infection as a means of delaying progression to end-stage liver disease (ESLD) and preventing the development of HCC. HCV is transmitted primarily through exposure to large amounts of blood or repeated direct percutaneous exposures to blood (i.e., transfusion or injection-drug use). HCV is not transmitted efficiently through occupational exposures to blood; the average incidence of anti-HCV seroconversion after accidental percutaneous exposure from an HCV-positive source is 1.8% (range: 0--7%), with one study indicating that transmission occurred only from hollow-bore needles [10] .Transmission rarely occurs through mucous membrane exposures to blood, and in only one instance was transmission in a health-care provider attributed to exposure of nonintact skin to blood [11] .The risk for transmission from exposure to fluids or tissues other than HCV-infected blood has not been quantified but is expected to be low. The exact duration of HCV viability in the environment is unknown but is at least 16--23 hours.

Since the discovery of HCV in 1989 [12] strategies to eradicate HCV have evolved rapidly. The need for a simple therapeutic regimen with fewer side effects allowing lower dropout rates, and improved overall efficacy cannot be over emphasized.

A cure is defined as a sustained virologic response (SVR) and consists of undetectable levels of plasma HCV RNA 12 or 24 weeks after therapy completion . Sustained virologic response (SVR) is defined as the absence of detectable levels of plasma HCV RNA 12 weeks after the completion of therapy .Patients who achieve SVR have stable virologic remission over the years following treatment and experience reversal of liver fibrosis and better liver-related outcomes [13] .SVR is therefore the equivalent to successful treatment of HCV. In monoinfected individuals, SVR has been linked to a decrease liver-related morbidity such as: decrease in liver decompensation, decrease in required liver transplantation, incidence of HCC and a decrease in all cause and liver-related mortality [14] . No vaccine exists to prevent HCV infection [15].Treatment for HCV infection is costly, and people who inject drugs (PWID) are less likely to receive medical monitoring and treatment of the infection than other patient groups [16] .The field of HCV therapeutics is evolving to develop strategies for eradicating HCV without using interferon formulations and/or ribavirin. This change simplifies treatment, improves tolerability, and decreases therapy duration, all while maintaining or increasing rates of SVR.

The treatment of chronic hepatitis C virus infection is rapidly evolving with the entry into the therapeutic armamentarium of a series of new and highly effective direct antiviral agents, targeted to the different virus structures involved in hepatitis C virus replication and assembly [17]. A breakthrough has taken place since the approval of the first direct-acting antivirals (DAA) in 2011. In addition to telaprevir and boceprevir, in 2014 two new NS3 protease inhibitors (simeprevir and faldaprevir), one non-nucleoside polymerase inhibitor (sofosbuvir) and one NS5a replication complex inhibitor (daclatasvir) have expanded the treatment options for chronic hepatitis C [18] . Sofosbuvir is considered, without controversies, the most promising single direct antiviral agent in the current scenario [17].

## MATERIALS AND METHODS

This systematic review was conducted according to PRISMA guidelines [19] .

Published research was scanned by formal searches of Web of Science, Scopus, Embase, Agricola, Cochrane Library, Cinahl Plus, Google Scholar, and Oaister from 1990 to 2016.

Search terms included “hepatitis C”, “antiviral agents”, “clinical trials” AND “ Phase II or Phase III or Phase V .

Citations were screened and evaluated using the established inclusion and exclusion criteria at the abstract level by two reviewres, and relevant studies were retrieved as full manuscripts. Articles were restricted to English language.

### 1.1. Eligibility criteria

***Inclusion criteria***

1. Patients with chronic HCV infection and;
2. Provision of treatment for hepatitis C in the
3. Randomized clinical trials and relevant cohort studies were included if they were published in English
4. Used FDA-approved therapies that included SVR as a primary or secondary end point.
5. Measuring and reporting either treatment uptake
6. or SVR outcomes.

***Exclusion criteria***

- Dose-finding studies

- Patients undergoing liver transplant, acute HCV, and HCV genotypes other than 1 through 3.

**Peer Review Process: a**n external group of experts reviewed a draft report detailing the methods and results of our review.

**RESULTS**

Electronic searches identified 437 publications in addition to another 17 publications that were found through manual search. After removal of duplicates, abstracts and titles 484 publications were assessed as identified from title and abstract, and 54 papers were excluded. There were 22 papers full text could not be retrieved , also 198 papers excluded because they did not discuss the present study's relevant endpoint (treatment and management of HCV genotype 1 through 3 ) and another 134 papers excluded for having the same cohort. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in reporting the results (**Figure 1)** [19]**.**

**Finally, 27 publications were selected to be studied in the present review.**

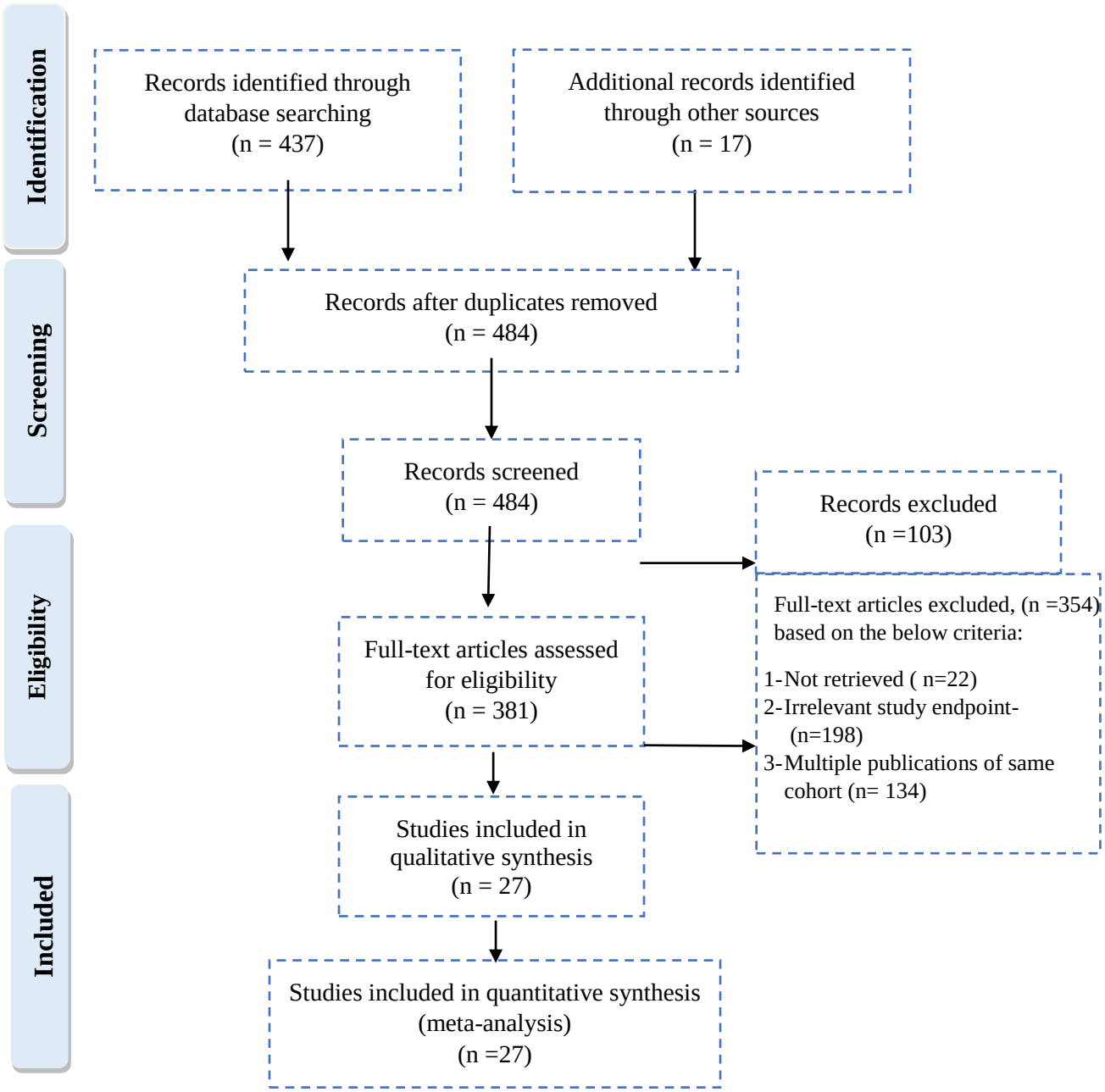


**Figure 1: PRISMA flow diagram showing the selection process and steps of the literature search.**

## *I. Genotype 1 treatment protocols*

### 1. Pegylated Interferon + Ribavirin (Weight-Based)+ Telaprevir/ Boceprevir

Boceprevir and telaprevir are selective HCV nonstructural protein (NS) 3/4A serine protease inhibitors. These drugs were the first DAAs developed and found to be effective in treating patients with HCV genotype 1. Based on the outcome of SVR, 7 evidence level 1B RCTs demonstrate the superiority of triple therapy using telaprevir [20, 21,22] or boceprevir [23,24] with pegylated interferon + weight-based ribavirin (1 g/d for ≤75 kg and 1.2 g/d for >75 kg) for the treatment of HCV genotype 1 treatment-naive patients (SVR range, 61%-75%) compared with treatment with pegylated interferon + weight-based ribavirin (SVR range, 38%-49%) [21,25,26]

Shortened durations (24 weeks for telaprevir- and 28 weeks for boceprevir-containing regimens) for patients who achieve rapid viral load declines within the first 12 weeks of therapy are as effective as fixed-duration therapy of 48 weeks[20,25] .

Four evidence level 1B RCT and 2 level 2B studies evaluated telaprevir [27,28,29] or boceprevir [25] + pegylated interferon + weight-based ribavirin in treatment-experienced patients. Previous partial responders and patients who relapsed had significant improvement in SVR rates when treated with telaprevir- or boceprevir-containing regimens for up to 48 weeks (SVR range, 69%-83%) compared with pegylated interferon + weight-based ribavirin alone (SVR range, 20%-29%). Previous null responders had modest increases in SVR rates with telaprevir-based therapy (SVR range, 39%-56% vs 9%-17%)

### 2. Pegylated Interferon + Ribavirin (Weight-Based)+ Simeprevir

Two DAAs, simeprevir and sofosbuvir, were recently approved for treating HCV. Simeprevir, an HCV NS3/4 serine protease inhibitor, was evaluated in treatment-naive patients and patients who had relapsed in 4 evidence level 1B studies[30,31] and 1 level 2B study, [32] showing higher rates of SVR (79%-86%) using 12 to 24 weeks of simeprevir + 24 to 48 weeks of pegylated interferon + weight-based ribavirin compared with pegylated interferon + weight-based ribavirin alone (SVR range, 37%-65%). In one representative study, 88% of participants had an early viral load decline (HCV RNA less than quantifiable at weeks 4 and undetectable at week 12) and were eligible for a shortened total duration of therapy of 24 weeks, with 83% to 88% of patients achieving SVR[31] .Patients without an early viral load decline were less likely to achieve SVR (range, 22%-32%) [31] .

One evidence level 1B study [33] of simeprevir in previous null and partial responders and relapsers showed that 12 to 48 weeks of simeprevir + pegylated interferon + weight-based ribavirin for 48 weeks resulted in high rates of SVR (67%-80%) compared with pegylated interferon + weight-based ribavirin alone (36%). Response rates to simprevir-containing therapy, however, were lower in null responders (41%-59% vs 19%) and partial responders (65%-86% vs 9%) than previous relapsers (76%-89% vs 37%) but higher compared with pegylated interferon + weight-based ribavirin. In both treatment-naive and treatment-experienced patients infected with HCV genotype 1a, those with a Q80K polymorphism in the NS3 region of hepatitis C virus responded less well to simeprevir-containing therapy (26%-31% difference in SVR).

### 3. Pegylated Interferon + Ribavirin (Weight-Based)+ Sofosbuvir

Sofosbuvir, an HCV NS5b nucleotide polymerase inhibitor, has been approved for treating HCV infection. Two evidence level 1B studies38,39 and 1 level 2B study40 showed high SVR rates (89%-90%) after treatment with only 12 weeks of sofosbuvir + pegylated interferon + weight-based ribavirin in treatment-naive patients. There was no benefit to extending treatment duration to 24 weeks or use of response-guided therapy (SVR range, 89%-91%) [34,35] .

## *II. Genotype 1, 2, and 3 treatment protocols*

An evidence level 1B study [36] among patients with HCV genotypes 2 and 3 demonstrated improved response to sofosbuvir + weight-based ribavirin therapy for 12 weeks compared with pegylated interferon + weight-based ribavirin for 24 weeks (97% with sofosbuvir vs 78% with pegylated interferon) in treatment-naive patients with HCV genotype 2. This high SVR rate in patients with HCV genotype 2 treated with sofosbuvir + weight-based ribavirin was confirmed in another evidence level 2B study[37] .One level 1B study[38] and 1 level 2B[37] study showed a benefit in longer-duration therapy (12 weeks vs 16 weeks) with sofosbuvir + ribavirin for treatment-experienced patients with

HCV genotype 3 (30% vs 62%) and an even larger benefit with 24 weeks of therapy in patients with HCV genotype 3 who were treatment experienced (80%) and treatment naive (95%) but not in patients with HCV genotype 2 (82% for treatment-experienced and 89% for treatment-naive).

Sofosbuvir + ribavirin for 12 to 24 weeks in HCV genotype 1 was evaluated in 2 evidence level 2B studies [39] . Response to treatment in patients with HCV genotype 1 who were treatment naive was 68% to 84%.

### *III. Special Populations*

#### 1. Patients With HIV-HCV Coinfection

About one-third of all HIV-infected patients are also coinfected with HCV [40] . Response rates to pegylated interferon + weight-based ribavirin in 2 evidence level 2B studies [41] were poor in treatment-naive and treatment-experienced coinfected patients (36%-15%). Two evidence level 1B studies[42] showed that the addition of telaprevir or boceprevir to pegylated interferon + weight-based ribavirin (SVR rates, 74% and 63%) was superior to pegylated interferon + weight-based ribavirin alone (SVR rates, 30% and 45%). However, sofosbuvir + weight-based ribavirin therapy for 24 weeks resulted in high response rates in patients with HCV genotypes 1, 2, and 3 (SVR range, 76%-92%) in 1 evidence level 2B study[37] .

To conclude, the addition of DAAs to pegylated interferon + ribavirin leads to significant improvements in SVR rates. The regimen of sofosbuvir + ribavirin has high SVR rates in small studies of patients with HIV-HCV coinfection.

#### 2. Patients With Compensated Cirrhosis

Few patients with compensated cirrhosis (ie, without jaundice, ascites, encephalopathy, or variceal hemorrhage) have been included in clinical trials of regimens using new DAAs, and patients with signs of portal hypertension (as evidenced by a platelet count $<90\times103/\mu L$) are generally excluded. In 4 studies,[30,21,25] treatment-naive patients with cirrhosis treated with telaprevir-containing therapy (62%-63% vs 75%) or boceprevir-containing therapy (41%-52% vs 67%-76%) had lower response rates than patients without cirrhosis. In a subanalysis of 1 study[36] of sofosbuvir + pegylated interferon + weight-based ribavirin for 12 weeks, patients with cirrhosis responded less well than patients without cirrhosis (80% vs 92%). Similarly, response to sofosbuvir + weight-based ribavirin alone for 24 weeks in patients with HCV genotype 1 was lower in patients with stage 3 or 4 liver disease (54% vs 79% with stage 2 or lower diease).[42] Response to treatment with simeprevir + pegylated interferon + weight-based ribavirin was lower in patients with bridging fibrosis or cirrhosis compared with those with less liver fibrosis for both treatment-naive patients (68% vs 84%) and treatment-experienced patients (73% vs 82% in previous relapsers, 67% vs 79% in partial responders, and 33% vs 66% in null responders)[31,33] .

These differences were not observed among patients with HCV genotype 2 who were treated with 12 weeks of sofosbuvir + weight-based ribavirin (83%-94% with fibrosis vs 92%-97% without fibrosis). Extending the duration of sofosbuvir + weight-based ribavirin combination therapy for treatment-naive patients with HCV genotype 3 from 12 weeks to 24 weeks improved SVR rates for patients with cirrhosis (21% vs 92%). This extended duration also resulted in a higher response rate in treatment-experienced patients with cirrhosis (SVR, 60%); however, this rate is still lower than that seen in treatment-experienced patients without cirrhosis (SVR, 85%) who were treated for the same duration[36,37,38] .

### *IV. Other Populations*

Few data are available regarding the use of directly acting antivirals (DAAs) in patients with impaired renal function (ie, glomerular filtration rate <50) or end-stage renal disease. This group may be at an increased risk of adverse events, particularly anemia in regimens containing ribavirin, and may require dose reductions in medications. No DAAs have been studied or are approved for use in children.

## DISCUSSION

In this systematic review, we attempted to address key questions regarding the treatment of chronic hepatitis C, we systematically reviewed RCTs regarding HCV treatment options for patients with different HCV genotypes. Treatment of HCV has evolved significantly and has led to improved rates of SVR. Improvement in HCV therapy began with the addition of the protease inhibitors telaprevir and boceprevir to pegylated interferon + weight-based ribavirin for patients with HCV genotype 1. These have now been replaced by sofosbuvir and simeprevir, with

improved efficacy and safety for treating HCV genotype 1. Sofosbuvir + weight-based ribavirin alone has replaced interferon-containing therapy for HCV genotypes 2 and 3.

Current evidence indicates that treatment for HCV genotype 1 should consist of sofosbuvir + pegylated interferon + weight-based ribavirin for 12 weeks (treatment-naive patients: grade A recommendation; treatment-experienced patients: grade B recommendation) because of the short duration of overall therapy. A second-line alternative in treatment-naive patients and previous relapsers is pegylated interferon + weight-based ribavirin for 24 weeks along with simeprevir for the first 12 weeks (grade A recommendation). Partial and null responders can be treated with pegylated interferon + weight-based ribavirin for 48 weeks along with simeprevir for the first 12 weeks (grade A recommendation). All therapy in patients who receive simeprevir-containing regimens should be stopped for patients with an inadequate on-treatment virologic response (ie, quantifiable HCV viral load at week 4, 12, and/or 24) (grade B recommendation). Prior to treatment with simeprevir-containing regimens, patients with HCV genotype 1a should be tested for the presence of a Q80K mutation, which reduces the likelihood of treatment success.

Patients infected with HCV genotype 2 can be treated with sofosbuvir + weight-based ribavirin for 12 weeks (treatment-naive patients: grade A recommendation; treatment-experienced patients: grade B recommendation). Patients infected with HCV genotype 3 can be treated with sofosbuvir along with weight-based ribavirin for 24 weeks (treatment-naive and -experienced patients: grade B recommendation).

Sofosbuvir + weight-based ribavirin had SVR rates similar in patients with HIV-HCV coinfection to those seen in patients with HCV monoinfection for genotype 1 (76%), genotype 2 (88%), and genotype 3 (92%); however, few patients with HCV genotypes 2 and 3 were included in initial studies. The use of sofosbuvir and, to a larger extent, simeprevir, telaprevir, and boceprevir in HIV-infected patients is complicated by extensive drug interactions with HIV antiretrovirals[44] .Hence, patients with HIV-HCV coinfection should be treated only by an experienced physician after careful assessment for potential drug interactions and using the same recommended regimens for HCV monoinfection (grade B recommendation).

Prior to HCV treatment, the stage of liver fibrosis should be assessed by liver biopsy or noninvasive markers. Patients with cirrhosis should be referred to a specialist for evaluation of sequelae (ie, hepatocellular carcinoma, hepatic decompensation) [42] and HCV treatment using the same regimens for patients with compensated cirrhosis as patients without cirrhosis (grade B recommendation).

Given the prevalence of neutropenia and anemia for patients receiving interferon-containing therapy, patients should be monitored for 2 weeks after starting treatment and at least monthly thereafter for the duration of therapy.

Limitations of this review include that study populations included in RCTs of sofosbuvir and simeprevir as well as newer DAAs are not demographically reflective of all patients with HCV. In particular, only small numbers of patients with cirrhosis, patients previously treated, minority patients, and patients coinfected with HIV were included, limiting the generalizability of recommendations. Further studies are warranted to evaluate the optimal combinations of DAAs and treatment duration that maximize treatment efficacy and minimize adverse effects for all subgroups of HCV-infected patients, to assess for potential for drug interactions between DAAs and concomitant medications, and to elucidate the implications of antiviral resistance.

Changes to guidelines for treatment of HCV can be expected as new regimens, many of which do not include interferon and are not included in this review, are developed and receive FDA approval. These interferon-free regimens have shown high SVR rates with few adverse events in phase 3 trials[43] . In response to these rapidly emerging results, the Infectious Diseases Society of America and the American Association for the Study of Liver Diseases jointly released in 2014 a dynamic online clinical guidance that accommodates rapid updates, which should be used as a reference[45] .In addition, given the recently published Centers for Disease Control and Prevention guidelines recommending birth cohort screening for HCV infection, many new HCV diagnoses can be expected in the United States[46] .The burden of care in HCV treatment will likely overwhelm the capacity of US hepatologists and infectious disease physicians.

Hepatitis C virus–positive patients without cirrhosis who have few comorbidities may be treated in a primary care setting using interferon-free therapy. Primary care physicians will need to be familiar with potential adverse effects of new regimens. Patients with cirrhosis, decompensated liver disease, renal insufficiency, multiple concomitant medications or comorbidities, or HIV coinfection, as well as pediatric patients, should be referred to a subspecialist for evaluation of liver disease as well as potential drug-drug interactions prior to HCV treatment. An important aspect of HCV not covered in this review is the cost of emerging DAAs. At the moment, the cost of treatment for a patient with HCV genotype 1 may be as high as $150 000, which will likely restrict wide use of novel agents.

## CONCLUSION

A growing body of evidence suggests that recently developed HCV combined treatment modalities have transformed chronic HCV into a routinely curable disease being relatively available and well tolerated ,which can potentially reduce the need for liver transplantation and reduce HCV-related mortality. Treatment protocol for genotype1 is based on a combined regimen of Pegylated interferons with ribavirin and sofosbuvir or simeprevir while Sofosbuvir with ribavirin alone should be used to treat patients infected with HCV genotypes 2 and 3. Patients coinfected with human immunodefiency virus and HCV genotype 1 should be treated for HCV with pegylated interferons, ribavirin, and sofosbuvir by a physician with experience in treating this particular group of patients and familiar with potential drug interactions.

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